European Journal of Endocrinology (2011) **164** 585–590 ISSN 0804-4643

CLINICAL STUDY

Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency

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Abstract

Objective: The objective was to study the associations between serum selenium concentration and thyroid volume, as well as the association between serum selenium concentration and risk for an enlarged thyroid gland in an area with mild iodine deficiency before and after iodine fortification was introduced. Another objective was to examine the association between serum selenium concentration and prevalence of thyroid nodules.
Design: Cross-sectional study.
Methods: We studied participants of two similar cross-sectional studies carried out before (1997–1998, $n=405$) and after (2004–2005, $n=400$) introduction of iodine fortification. Serum selenium concentration and urinary iodine were measured, and the thyroid gland was examined by ultrasonography in the same subjects. Associations between serum selenium concentration and thyroid parameters were examined in multiple linear regression models or logistic regression models.
Results: Serum selenium concentration was found to be significantly, negatively associated with thyroid volume ($P=0.006$), and a low selenium status significantly increased the risk for thyroid enlargement ($P=0.007$). Furthermore, low serum selenium status had a tendency to increase the risk for development of multiple nodules ($P=0.087$).
Conclusions: Low serum selenium concentration was associated with a larger thyroid volume and a higher prevalence of thyroid enlargement.

European Journal of Endocrinology **164** 585–590

Introduction

Both iodine and selenium play an important role in the function of the thyroid gland (1). Iodine is a main constituent of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). Selenium is found in high concentration in the thyroid gland, thus suggesting an important contribution of selenoproteins to integrity and function of the gland (2–4). Selenium is incorporated as selenocysteine into a number of antioxidant selenoproteins and contributes to the antioxidant defense by protecting the thyrocytes from any excess hydrogen peroxide, which is produced during thyroid hormone biosynthesis (5, 6). In addition, selenium constitutes an essential part of the iodothyronine deiodinase enzymes, which catalyze thyroid hormone by activation and inactivation (4, 5). Thus, selenium deficiency may result in a decreased conversion of T_4 to the active hormone T_3.

Myxedematous endemic cretinism is prevalent in goiter-endemic countries with low selenium and glutathione peroxidase concentrations in serum (7). However, selenium may also be important for optimal thyroid functioning and regular thyroid hormone action in areas without cretinism, given the fact that a negative correlation between serum selenium and thyroid volume was reported for children living in an endemic goiter area (8). Results of other studies have not been consequent; both an inverse association (9) and no association have been found (10) between urinary selenium and thyroid volume. Likewise, both an inverse (11) and no association (9) have been found between serum selenium concentration and thyroid volume.

In the present study, the association between serum selenium concentration and thyroid volume was investigated both before and after iodine

DOI: 10.1530/EJE-10-1026
Online version via www.eje-online.org

fortification was introduced in Denmark. Furthermore, associations between serum selenium concentration and risk for enlarged thyroid gland and the risk for thyroid nodules were investigated.

Subjects and methods

Subjects were participants in the Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr). In this study, two cross-sectional studies have been carried out, the first (C1) in 1997–1998 and the second (C2) in 2004–2005. The cross-sectional studies took place at two centers located in the cities of Aalborg (situated in the western part of Denmark) and Copenhagen (situated in the eastern part of Denmark) respectively. For both studies, a random sample of people within selected age and sex groups living in the two cities was drawn from the Civil Registration System as described in detail previously (12, 13). In C2, the sample excluded subjects participating in C1. For the present study, we randomly selected participants from the groups: women aged 18–22, 40–45, and 60–65 years, and men aged 60–65 years. In C1, participation rate was 50.1%, and in C2, participation rate was 46.6%. Equal numbers from the two cities were selected. Data analyses were performed on 805 participants (405 from C1 and 400 from C2) from which all the variables of interest were available. Both studies were approved by the regional ethical committees, and all participants provided written, informed consent.

All participants visited the center at either Copenhagen or Aalborg, and all participants completed a questionnaire, which gave information about individual smoking habits and alcohol consumption.

Thyroid volume and thyroid nodules

An ultrasonography was performed using a Sonoline Versa Pro 7.5 MHz 70 mm linear transducer (Siemens, Munich, Germany) with an effective length of 62 mm. Thyroid volume was calculated as maximal length × width × depth × π/6 of each lobe. Thyroid enlargement was defined as a thyroid volume > 18 ml for women and 25 ml for men, which corresponds to the mean + 3 S.D. values in iodine-sufficient populations (14). Records were made on distinct nodules larger than 10 mm in diameter. In the event of more than three nodules in a lobe, only the three largest nodules were registered. The structure of the gland was classified as normal, diffuse (no registered nodules), solitary nodule (one thyroid nodule), or multinodular (more than one thyroid nodule). The same two sonographers performed the ultrasonographies both before and after iodine fortification in the two cities respectively. Their comparability was studied and has been described elsewhere (15).

Urine samples

All participants were asked to give a urine sample when they visited the center. These casual urine samples were stored at −20 °C, and later analyzed for iodine and creatinine. Iodine excretion was expressed as estimated (est.) 24 h urinary iodine excretion. To calculate the est. 24 h urinary iodine excretion, we multiplied the iodine:creatinine ratio with the expected daily creatinine excretion for the given individual. The expected 24 h creatinine excretion was based on the data of Kesteloot & Joossens (16). A satisfactory agreement between est. 24 h urinary iodine excretion and observed 24 h urinary iodine excretion has been found (17, 18), and this estimate is a less variable indicator of iodine intake than spot urinary iodine concentration (19).

Iodine in urine was measured by the Ce-As method after alkaline ashing (20) as described previously (21). The intra- and inter-assay coefficients of variations (CV) for single determinations were 2.1 and 2.7% respectively.

Urinary creatinine was determined using Vitros creatinine slides and Vitros Chemistry Products calibrator kits on a Vitros 250 chemistry system (Ortho-Clinical Diagnostic System, Inc., Rochester, NY, USA). Intra- and inter-assay CV were below 5%.

Blood samples

Blood samples were obtained, and serum was stored at −20 °C. Serum selenium was determined in triplicate by a fluorimetric method described earlier (22). The limit of detection was 15 μg/l, allowing reliable analysis of human serum concentrations, which typically range between 50 and 200 μg/l. Inter-assay variation was 7%, and intra-assay variation was <5% during the determinations. Human seronorm serum standard (Sero AS, Billingstad, Norway) with selenium at 79 μg/l along with an atomic absorption selenite standard solution (Sigma–Aldrich Chemie GmbH) was used to control and standardize the analyses.

For all analyses, samples were analyzed in random order with respect to season, age, sex, and city, and for the analyses of serum selenium also with respect to cross-sectional study.

Statistical analyses

Comparisons of variables between C1 and C2 were done by *t*-test or for data not normally distributed with Mann–Whitney *U* test.

The relations between serum selenium concentration and thyroid volume were investigated in multiple linear regression models (general linear models) with log-transformed thyroid volume as the dependent variable. Apart from serum selenium concentration, the following variables were included in the models as confounders: age and sex group, smoking (daily

smoker or not), body surface area, iodine excretion, and cross-sectional study (if both cohorts were included in the analysis). Interactions between iodine and selenium, city and selenium, cohort (before versus after fortification) and selenium, age and selenium, and smoking and selenium were investigated.

The relationship between selenium status and thyroid enlargement and the relationship between selenium status and thyroid nodules were examined in logistic regression models. The same variables as described above were included in these models as independent variables. Data processing was done with SPSS version 14.0 (Chicago, IL, USA).

Results

Descriptions of the studied populations are shown in Table 1. Thyroid volume decreased significantly from the first to the second cross-sectional study, and urinary iodine excretion increased at the same time. Furthermore, median serum selenium concentration decreased slightly, but significantly, by 5% during this time period. Iodine excretion and serum selenium concentration were weakly but significantly positively correlated, $r=0.2$, $P<0.001$.

Thyroid volume

In the combined cohort, serum selenium concentration was significantly, negatively associated with thyroid volume (Table 2).

The association was only statistically significant in the cohort after iodine fortification had been introduced, but the same pattern was seen in both the cohort before and after iodine fortification (Table 2). The significant negative association between serum selenium concentration and thyroid volume was found in the entire group of women but did not reach significance in the subgroup of women being 60–65 years. In men (all 60–65 years), there was no association between thyroid volume and serum selenium concentration (Table 2).

No difference in the association between thyroid volume and serum selenium concentration was observed between the two cities ($\beta=-0.002\pm0.001$, $P=0.085$ and $\beta=-0.003\pm0.001$, $P=0.082$ in the city with mild and moderate iodine deficiency respectively).

No significant interactions between serum selenium concentration and iodine status, city, cohort (before versus after fortification), or sex on thyroid volume were found.

Thyroid enlargement

Serum selenium concentration was significantly, negatively associated with risk for enlarged thyroid gland (Table 3). The association was significant before iodine fortification, but not after iodine fortification (Table 3). Furthermore, the risk for enlarged thyroid gland increased with lower serum selenium concentration in women but not in men (Table 3).

Thyroid nodules

Low serum selenium concentration tended to increase the risk for multiple nodules of more than 10 mm in diameter ($\beta=-0.010\pm0.006$, $P=0.087$ (number with multiple nodules $n=114$)). In contrast, serum selenium did not influence the risk for solitary nodules ($\beta=0.001\pm0.007$, $P=0.855$, number with solitary nodules $n=53$).

Discussion

Low serum selenium concentration was found to be weakly associated with a larger thyroid volume, a higher risk for enlarged thyroid gland and for development of multiple thyroid nodules. This association was found in women, whereas serum selenium showed no association to thyroid gland size in the smaller group of men studied.

Results from other studies examining the relation between selenium and thyroid volume differ (8–10, 23–28). However, the results from our study are in line with results from the largest study carried out so far regarding selenium and thyroid volume (11). Here, by using multiple linear regression models, a significant

Table 1 Descriptive parameters of the cohorts studied.

	Before fortification, C1 ($n=405$)	**After fortification, C2** ($n=400$)	**All** ($n=805$)
Thyroid volume (ml)	12.5 (9.5, 17.3)	11.9 (8.5, 16.3)*	12.2 (8.9, 16.9)
Est. 24 h iodine excretion (μg/day)	97 (60, 181)	148 (106, 240)†	124 (78, 211)
Urinary iodine concentration (μg/l)	57 (34–91)	100 (56–154)	74 (43–128)
Serum selenium (μg/l)	99.2 (88.1, 112.0)	95.0 (85.0, 104.4)*	96.8 (86.2, 107.9)
Enlarged thyroid, number (%)	72 (17.8%)	57 (14.3%)	129 (16.0%)
Multiple thyroid nodules, number (%)	52 (12.8%)	61 (15.3%)	113 (14.0%)
Solitary thyroid nodule, number (%)	30 (7.4%)	23 (5.8%)	53 (6.6%)

Results are median (25 and 75 percentiles). *$P<0.05$, †$P<0.001$ compared with first cross-sectional study (C1) (Mann–Whitney U test).

Table 2 Association between serum selenium concentration and thyroid volume. General linear models[a] with log thyroid volume as the dependent variable and serum selenium concentration as the independent variables.

	Serum selenium (slope ± S.D.)[a]
All (n=805)	$\beta = -0.002 \pm 0.001$, P=0.006
Before fortification, C1 (n=405)	$\beta = -0.001 \pm 0.001$, P=0.144
After fortification, C2 (n=400)	$\beta = -0.003 \pm 0.002$, P=0.031
Women (n=654)	$\beta = -0.003 \pm 0.001$, P=0.004
Women 60–65 years (n=228)	$\beta = -0.002 \pm 0.002$, P=0.113
Men 60–65 years (n=151)	$\beta = -0.001 \pm 0.002$, P=0.734

[a]The models include age and sex group, smoking (daily smoker or not), drinking (≥8 drinks/week or <8 drinks/week), body surface area (BSA), and cross-sectional study.

negative association between serum selenium and thyroid volume was observed in 1100 women but not in the 792 men who participated. The iodine intake was comparable to the intake in the present study, but the serum selenium concentration was lower, on average 87 μg/l.

The effect of selenium on thyroid volume was not clearly related to iodine status within the present population without severe iodine deficiency at any time. It is being discussed whether selenium only has an influence on the thyroid in populations with iodine deficiency or also shows effect in populations with sufficient iodine intake. The effect of selenium on the thyroid gland and thyroid function in severe iodine deficiency is likely to be more pronounced than in mild iodine deficiency (28). In line with this, thyroid weight was not different in selenium-deficient and selenium-supplemented rats that received iodine supplementation, whereas selenium deficiency further increased the thyroid weight in iodine-deficient rats (29). Whether the same applies to humans cannot be concluded from the studies carried out so far, as the studies have included various groups according to age, gender, and severity of iodine deficiency, and the data have been collected and analyzed in different ways. Furthermore, other factors that might influence thyroid volume have not always been taken into account. However, the present study as well as the study from France (11), which both took other factors into account and were carried out in areas with mild iodine deficiency, found a negative association between selenium status and thyroid volume in women.

The impact of selenium on the thyroid gland seems to differ in men and in women. In the present study, we did not find an association between serum selenium and thyroid volume in men. Although the smaller sample of men in our study could explain the missing association, we still found some significant associations in the subgroup of women 60–65 years of age. A sex difference is in agreement with the results of the study by Derumeaux *et al.* (11). Furthermore, Ozata *et al.* (26) did not find a difference in serum selenium between men with goiter and men without goiter. The sex difference could explain part of the inconsistency in the results from different studies. Similar sex-specific differences have been observed in experimental animals where selenoprotein biosynthesis differs in a tissue-specific manner between male and female mice (30). The molecular reason why women seem to be more susceptible to a low selenium concentration than men is not known, but thyroid diseases are in general more common in women than in men (12). Another reason for the inconsistency between studies could be the age of the included subjects. Age has also been described to represent an important factor for the sexual dimorphic selenoprotein biosynthesis in experimental mice (31). Furthermore, an inter-relationship of plasma selenium with sex hormone secretion has been reported (32).

Samir & el-Awady (25) found lower serum selenium concentrations in 22 subjects with multinodular goiter compared with 15 control subjects. Derumeaux *et al.* (11) did not find increased risk for nodules in subjects with low serum selenium; however, the study did not distinguish between the effect on multinodular and solitary nodule development. We found a tendency to higher occurrence of multiple nodules with lower serum selenium concentration but no association between serum selenium concentration and the occurrence of solitary nodules. An interaction between smoking and iodine intake has previously been found on thyroid nodules (33), but we did not find an interaction between smoking and selenium status on nodules.

There are a number of potential molecular mechanisms underlying the increased risk of goiter in subjects with lower selenium status. The selenocysteine-containing active selenoproteins, such as iodothyronine deiodinases, are likely to be responsible for the observed interrelation as they are presumably converting the effects of selenium into biological processes (34). In line with this, a weak negative correlation between serum selenium concentration and T_4 or free T_4 (fT_4) has been found (9, 35), but an effect of selenium supplementation on T_4 concentration has only been found in few studies (36). In general, we did not find an association between selenium status and fT_4, which could indicate that

Table 3 Association between serum selenium concentration and thyroid enlargement. Logistic regression models[a] with thyroid enlargement (thyroid volume >18 ml for women and >25 ml for men) as the dependent variable.

	Serum selenium (slope ± S.D.)[a]
All (n=805)	$\beta = -0.017 \pm 0.006$, P=0.007
Before fortification, C1 (n=405)	$\beta = -0.019 \pm 0.008$, P=0.021
After fortification, C2 (n=400)	$\beta = -0.012 \pm 0.010$, P=0.249
Women (n=654)	$\beta = -0.023 \pm 0.009$, P=0.013
Women 60–65 years (n=228)	$\beta = -0.023 \pm 0.010$, P=0.021
Men 60–65 years (n=151)	$\beta = -0.006 \pm 0.014$, P=0.649

[a]The models include age and sex group, smoking (daily smoker or not), drinking (≥8 drinks/week or <8 drinks/week), body surface area (BSA), and cross-sectional study.

selenium status in Denmark is adequate for optimal activity of the deiodinases (results not shown). Besides the deiodinase enzymes controlling the thyroid hormone metabolism, the family of selenium-dependent antioxidative glutathione peroxidases are prime candidates for the observed association between selenium status and thyroid volume because they are abundantly expressed within the thyroid gland (3) and strongly depend on the selenium status to be sufficiently expressed (1, 6).

We can conclude that serum selenium concentration has an effect on thyroid volume and probably multiple nodule formation in areas with mild iodine deficiency; however, the association is weak and appears to be confined to women.The results of the present study as well as some previous studies suggest that sufficient selenium intake is one of the environmental factors that may add in the prevention of goiter and thyroid nodules. Prospective intervention studies are needed to evaluate the potential role of selenium in patients suffering from goiter and thyroid nodularity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The study was supported by grants from Tømmerhandler Vilhelm Bang Foundation, the Copenhagen Hospital Cooperation Research Foundation, the 1991 Pharmacy Foundation, the Danish Medical Foundation, The Health Insurance Foundation, North Jutland County Research Foundation, Musikforlæggerne Agnes og Knut Mørks Foundation, the German Research Foundation (DFG; GraKo 1208, Scho 849/2-2), the German Cancer Aid (Deutsche Krebshilfe, 10-1792 Scho2), The Danish Medical Research Council, and The Danish Food Industry Agency.

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Received 14 January 2011
Accepted 17 January 2011